ART 34 AMDT

WHAT IS CLAIMED IS:

1. An *in vitro* model of a mammalian tissue, said model comprising living mammalian cells of at least two different phenotypes in a predetermined initial proportion, the cells of at least one phenotype forming 3-dimensional aggregates, wherein the cells are allowed to proliferate and wherein the proliferation kinetics of the cells of at least two different phenotypes is simultaneously assessed.

2. A model according to claim 1, wherein the 3-dimensional cell aggregates are of an essentially spheroidal shape.

3. A model according to claim 1, wherein the 3-dimensional cell aggregates are formed in the absence of a solid support.

4. A model according to claim 1, wherein the 3-dimensional cell aggregates are formed in the presence of a solid support.

5. A model according to claim 4, wherein the solid support consists of porous beads.

6. A model according to claim 1, wherein the proliferation kinetics is measured using fluorescent labeling of cells of at least one phenotype.

7. A model according to claim 6, wherein the cells are fluorescently labeled prior to being allowed to proliferate.

8. A model according to claim 7, wherein the cells are labeled with a fluorescent membrane linker.

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9. A model according to claim 7, wherein the cells are labeled by loading with a fluorescent dye.

10. A model according to claim 1, wherein the 3-dimensional aggregates comprise cells of a first and of a second phenotype.

11. A model according to claim 10, wherein the cells of at least one phenotype are fluorescently labeled prior to forming the 3-dimensional aggregates.

12. A model according to claim 11, wherein the cells are labeled with a fluorescent membrane linker.

13. A model according to claim 11, wherein the cells are labeled by loading with a fluorescent dye.

14. A model according to claim 13, wherein the dye is calcein-AM.

15. A model according to claim 12, wherein the cells of the first and the second phenotype are labeled with fluorescent membrane linkers fluorescing at different wavelengths.

16. A model according to claim 10, wherein the cells of the first and the second phenotype are of human origin.

17. A model according to claim 16, wherein the cells of the first phenotype are normal cells of human origin.

18. A model according to claim 17, wherein the cells of the first phenotype are endothelial cells.

19. A model according to claim 18, wherein the cells of the second phenotype are tumour cells.

20. A model according to claim 19, wherein the endothelial cells are fluorescently labeled.

21. A model according to claim 20, wherein the endothelial cells are labeled with a fluorescent membrane linker.

22. A model according to claim 21, wherein the 3-dimensional cell aggregates are formed in the absence of a solid support.

23. A model according to claim 21, wherein the 3-dimensional cell aggregates are formed by growing a layer of the endothelial cells on particles of a solid support and then seeding the tumour cells to the layer of endothelial cells.

24. A model according to claim 23, wherein the solid support is capable of releasing a blood substitute.

25. A model according to claim 17, wherein the cells of the first phenotype are stromal cells.

26. A model according to claim 25, wherein the cells of the second phenotype are tumour cells matching the source of the stromal cells.

27. A model according to claim 26, wherein the cells of both phenotypes are fluorescently labeled with labels fluorescing at different wavelengths.

28. A model according to claim 27, wherein the labels are fluorescent membrane linkers.

29. A model according to claim 28, wherein the 3-dimensional cell aggregates are formed in the absence of a solid support.

30. A model according to claim 28, wherein 3-dimensional aggregates are formed by growing a layer of the stromal cells on particles of a solid support and then growing a layer of the tumour cells on the layer of the stromal cells.

31. A model according to claim 17, wherein the cells of the second phenotype are tumour cells.

32. A model according to claim 31, wherein the cells of the first phenotype are cells of a tissue in which metastases of the tumour are expected to develop.

33. A model according to claim 32, wherein the cells of the first phenotype are epithelial cells.

34. A model according to claim 33, wherein the cells of the first phenotype are grown as a monolayer on one side of a porous solid support.

35. A model according to claim 34, wherein the tumour cells in the form of 3-dimensional aggregates are applied to the opposite side of the support.

36. A model according to claim 35, wherein the tumour cells are fluorescently labeled.

37. A model according to claim 16, wherein the cells of the second phenotype are cells of the first phenotype treated with a chemical agent prior to forming the 3-dimensional aggregates.

38. A model according to claim 37, wherein the chemical agent is capable of blocking the proliferation of cells without killing the cells.

39. A model according to claim 38, wherein the chemical agent is mitomycin.

40. A model according to claim 37, wherein the chemical agent is a phototoxic agent.

41. A model according to claim 40, wherein the chemical agent is chloromethyl eosine diacetate.

42. A model according to claim 41, wherein the 3-dimensional aggregates of cells are illuminated with a light source after formation.

43. A method of screening for an antitumour substance, said method comprising the steps of:
    a. providing an *in vitro* model of human tissue according to claim 1, said model comprising at least one phenotype of tumour cells;
    b. providing a candidate antitumour substance;
    c. allowing the cells to proliferate for a predetermined period of time, in the presence and in the absence of the candidate antitumour substance;
    d. measuring the cell proliferation rate of at least one cell phenotype in the absence and in the presence of the candidate antitumour substance; and
    e. accepting or rejecting the candidate antitumour substance based on results of the measurements of step d.

44. A method according to claim 43, wherein cells of at least one cell phenotype are fluorescently labeled.

45. A method according to claim 44, wherein cells are labeled with a fluorescent membrane linker.

46. A method according to claim 45, further including the step of dispersing the cell aggregates into a suspension of individual cells prior to measuring the cell proliferation rate.

47. A method according to claim 46, wherein the proliferation rate is expressed as the proliferation index.

48. A method according to claim 47, wherein the proliferation index is calculated from a flow cytometry analysis of the cell suspension.

49. A method of screening for a substance modulating gap junction intercellular communication, said method comprising the steps of:
   a. providing an *in vitro* model of a human tissue according to claim 1, said model comprising at least one cell phenotype loaded with a fluorescent dye impermeant to the cell membrane;
   b. providing a candidate modulating substance;
   c. culturing the cells for a predetermined period of time, in the presence and in the absence of the candidate substance;
   d. measuring the migration of the dye to at least one other cell phenotype, in the absence and in the presence of the candidate substance modulating gap junction intercellular communication; and
   e. accepting or rejecting the candidate modulating substance based on results of the measurements of step d.

50. A method according to claim 49, further including the step of dispersing the cell aggregates into a suspension of individual cells prior to measuring the migration of the dye.

51. A method according to claim 50, wherein the dye is calcein-AM.

52. A method for predicting a biological characteristic of a mammalian tissue, said method comprising the steps of:

a. providing a cellular automaton simulation model of the mammalian tissue;
b. setting model parameters;
c. running the model; and
d. evaluating the biological characteristic of the tissue based on results of step c.

53. A method according to claim 52, wherein the simulation model is SIMCEL-2D or SIMCEL-3D simulation model.

54. A method according to claim 53, wherein the biological characteristic of a mammalian tissue is the cyclic cell recruitment from the resting pool, the cell proliferation index, or intercellular diffusion.

55. A method according to claim 54, wherein the model parameters are set to simulate effects of physical or chemical agents on the tissue.